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ORIGINAL ARTICLE

Adapalene in the treatment of African patients

WK Jacyk

Department of Dermatology, University of Pretoria, PO Box 667, Pretoria 0001, South Africa. tel. +27 12 354 2375; fax +27 12 354 1856

ABSTRACT

Aim To assess the efficacy and safety of topical adapalene gel 0.1% as a treatment for acne vulgaris in black South African patients.

Background African and other darker skin types represent a particular clinical challenge for dermatologists treating acne. In many cases, this is due to the higher risk of postinflammatory hyperpigmentation in patients with dark skin. Acne vulgaris is an extremely common dermatological problem among Africans and people of African descent worldwide. Few studies of any of the major acne therapies have been carried out in exclusively black populations, and relatively little is known about the specific responsiveness of black skin to these agents. The ideal acne treatment for black people would specifically target the inflammatory process, which so often results in hyperpigmentation. Topical retinoids do this to some degree, but they can be highly irritating and this in itself can provoke post-treatment hyperpigmentation.

Methods An open-label study of adapalene 0.1% gel in 65 black South Africans, aged 12–30, for 12 weeks. Patients all had mild to moderate facial acne as defined by the Leeds scoring system; they were instructed to apply the medication once daily. Lesion counts and severity scores were assessed at 4, 8 and 12 weeks.

Results A total of 44 subjects completed the trial and all three follow-up visits. Adapalene gel 0.1% showed clear efficacy against both inflammatory and non-inflammatory lesions. The drop in mean total facial-lesion count ranged from 46 to 72% between the first and last visit, and in most cases, there was clear improvement in cosmesis. In two-thirds of cases, patients experienced reductions in both number of hyperpigmented macules and density of hyperpigmentation.

Conclusion Adapalene gel 0.1% is an effective, well-tolerated topical therapy for black patients. It is able to reduce both inflammatory and non-inflammatory lesions, as well as prevent and alleviate acne-associated hyperpigmentation.

Key words: adapalene, acne vulgaris, acne in Africans

Introduction

The term 'black' skin is generally used in the dermatological literature to represent the cutaneous features characteristic of two very broad racial groups: natives of the African continent and African-Americans.[1]

Acne is a common problem worldwide, and while some studies have suggested that there may be small racial differences in the relative prevalence of specific types of acne, and variations in the clinical manifestations of the disorder between different racial groups, in general acne vulgaris appears to be more or less equally prevalent among blacks, whites, and Asians. However, the natural history, clinical course, and most importantly, the long-term sequelae of acne can be considerably different. All darker-skinned individuals are at increased risk of postinflammatory hyperpigmentation. Inflammatory processes are well recognized in the pathogenesis of acne vulgaris, and postinflammatory hyperpigmentation is a major acne sequela among black and Asian acne patients. In some cases, these long-lasting hyperpigmented lesions – not the active primary lesions – are the main reason these patients seek dermatological care.

In general, the acne therapies that are effective in white patients will be equally effective in black or other dark-skinned individuals. To date, however, dermatologists are lacking treatments that can prevent or resolve postinflammatory hyperpigmentation secondary to acne. The primary treatment for hyperpigmentation – hydroxyquinones, alone or in combination with benzoyl peroxide, retinoids or other acne medications – are slow in acting, only partially effective, highly irritating and capable of inducing hypopigmented 'haloes' around the

partially resolved hyperpigmented areas.[2,3] Topical and systemic retinoids are usually effective in resolving acne vulgaris among black patients and other dark-skinned individuals. But they can be highly irritating, sometimes inducing inflammation, and this itself can result in post-treatment hyperpigmentation.

Our open-label study of topical adapalene gel in black South African acne patients indicate that it is a safe, effective and minimally irritating treatment, with some potential to reduce postinflammatory hyperpigmentation.

Racial differences in skin physiology

Beyond the obviously greater concentration and distribution of melanocytes, there are a number of well-documented histological differences between black and white skin. Among black Africans or people of African descent, the stratum corneum tends to be highly compact, containing more but thinner corneocyte layers. The stratum corneum also tends to be more lipid-rich and contains greater numbers of stratum corneum melanosomes.[4] However, there are no reported differences regarding the physiology of the pilosebaceous unit or level of sebum production in skin of colour as compared to white skin.

Black people tend to have more apocrine and eccrine glands in the skin, and a greater density of glycosylated proteins in the skin matrix. The papillary dermis is characterized by a higher population of macrophages which tend to be larger and more numerous than in white skin.[5] The fibroblasts are larger and more numerous, and the dermis of black skin tends to maintain its highly ordered structure and elasticity to a far greater extent than that of white skin. This is largely due to a reduced incidence of photoaging. All of these factors can influence the prevalence and the manifestation of dermatological disorders, including acne, in black vs. white populations.

Prevalence of acne in black vs. white populations

In general, this disease is not as well characterized among black people and other individuals of colour as it is in white people. A survey representing an estimated 24 million patient encounters by US dermatologists in 1990, indicated clearly that after adjusting for their proportion in the general population, US black and Native American people are far less likely to seek dermatological care than white people, Asians or Pacific Islanders.[5]

In the US, it appears that acne vulgaris is by far the most common form of dermatosis seen in African-American individuals seeking skin care. In a survey of the 12 most common dermatoses in a dermatological practice serving a predominately black population, acne vulgaris accounted for 27.7% of all cases, with eczema representing 20.3% and pigmentary problems accounting for 9% of cases.[6] The prevalence of acne vulgaris in this study did not differ significantly from that observed among white dermatological patients.

A recent survey from the UK involving 461 black patients attending a London dermatology clinic over a 3-month period showed that acne and acne keloidalis nuchae were the most common conditions for which adult patients sought care.[7] This echoes the pattern observed in the US. Acneiform eruptions accounted for 27.5% of all diagnoses in the 274 adult patients in this sample. In contrast, psoriasis was the most common diagnosis among white patients seeking care at the same clinic.

On the Caribbean island of Guadeloupe, which has a predominately black population, acne vulgaris was the most common diagnosis seen in a series of 5000 new patient encounters; it accounted for 16.4% of all new diagnoses, and there were no differences in the apparent prevalence of acne in black vs. white individuals.[8] This pattern may not be representative of the Caribbean in general; the economic standard of living tends to be higher among black people on Guadaloupe compared with other Caribbean islands, and this may affect the relative prevalence of various skin disorders.

Few surveys have compared the prevalence of acne among native black Africans with white people, either in Africa or on other continents. Clinical experience indicates that acne is fairly common among black people in South Africa. But a precise definition is difficult because there have been few large prevalence studies. What little data there are suggest that prevalence patterns of common dermatological disease may be somewhat different in southern Africa compared to other regions of the world.

In contrast to what has been reported in the US, a survey of skin presentations among 5000 black South Africans in Pretoria, showed that eczemas were the most common, accounting for 29% of all cases. Acne was the second most common, accounting for 11% of cases.[9] The same pattern of disease frequencies held for white South Africans, but the author noted that acneiform disorders were less common in the 'Indian' and 'coloured' ethnic subgroups in South Africa. The contrast between these observations and the patterns seen in US and UK surveys suggest either geographical variations in the prevalence of particular disorders, or cultural and economic variables that influence patients' decisions to seek care.

It appears that on average, the clinical presentation of acne vulgaris may be somewhat milder among US black individuals vs. white individuals, though the prevalence of comedonal and inflammatory acne is similar. In our clinical experience, severe nodulocystic acne is rare among black South Africans, and acne fulminans has not been reported at all. These differences have been reported in the US as well.[10,11]

Acne subtypes specific to black people

Certain types of acne and acneiform disorders are almost exclusively seen among black people. The so-called 'pomade acne' is a type of acne cosmetica characterized by closely packed, closed comedones, and related to the cosmetic practice

of applying oils and greases to the hair and skin. This practice is common in some black communities; some of the products used contain petrolatum, lanolin, mineral oils and oleic acids. All have been shown to be comedogenic in rabbit models.[13]

Acne keloidalis nuchae is not a true variant of acne but rather a form of folliculitis, usually seen on the back of the neck. It arises when *Propionibacterium acnes* colonizes ingrown terminal hairs. It is fairly common among black men, and often results in formation of grouped keloids.[12] This condition is almost never seen in white populations.

The challenge of acne and its sequelae in dark-skinned patients

On the surface, acne sometimes appears to be less severe in black patients compared with white patients. This is in part due to the fact that the erythematous changes associated with the inflammatory process may be somewhat masked by high melanin content. In truth, acne can be highly inflammatory in dark-skinned individuals. Pigmentary abnormalities, which can be persistent and disfiguring, are commonly associated with all skin disorders of an inflammatory nature in black people.[3] Given the propensity for black skin to develop hyperpigmentation and keloid formation, the secondary sequelae of inflammatory acne lesions may be as severe or worse than the primary lesions themselves. US investigators have reported that some patients may be more concerned about the hyperpigmented macules than the original lesions; unlike white patients, black patients often seek dermatological care for these secondary problems – which can be quite long-lasting – rather than for the acne lesions themselves.[13]

The mechanism driving the development of hyperpigmentation is related to a rise in skin temperature during the inflammatory cascade, which in turn increases the activity of tyrosinase. The action of this enzyme on tyrosine increases the production of dopa and other intermediary molecules, which ultimately polymerize to form melanin. The intensity of the postinflammatory hyperpigmentation is somewhat related to the intensity of the initial inflammation.[3] The postinflammatory hyperpigmentation may be confined to the dermis or it may also include the epidermis. Black patients with acne may show a wide variety of lesional morphologies at any given time: a patient may present with a simultaneous mixture of papules, pustules, comedones, hyperpigmented macules and keloids.[1]

Treatment strategies for dark-skinned patients with acne

The key pathogenic processes in the evolution of acne are: increased sebum production secondary to androgen stimulation, abnormal desquamation of the follicular epithelium, colonization of the affected follicle by *P. acnes*, and triggering of inflammatory reactions to bacterial antigens. In all patients, regardless of race, optimal therapy depends on addressing as many of these mechanisms as possible. But given the propensity of dark-skinned individuals for postinflammatory hyperpigmentation, it is critical to pay special attention to the inflammatory component of the process and to arrest formation of new inflammatory acne lesions.

The ideal acne therapy for dark-skinned individuals would not only speed resolution of extant lesions and prevent formation of new microcomedones, comedones and inflammatory lesions; it would also arrest the inflammatory processes, thus preventing or even resolving acne-related hyperpigmentation.

Retinoid therapy

Given the immunomodulatory effects of topical retinoid therapy, a number of investigators have studied this approach for treatment of acne and related hyperpigmentation in black people. As a class, retinoids are safe and effective for both topical and systemic acne therapy in these populations.

Halder recently conducted an 8-week, double blind vehicle-controlled study of topical tretinoin 0.025% cream, applied daily, in 27 patients with acne vulgaris. Among the 12 patients on active treatment, 87% had statistically significant decreases in papules, pustules and hyperpigmented macules vs. only 13% of the 15 patients using vehicle alone. As in nearly all topical tretinoin trials, irritation and inflammation were a problem for many patients.[1] Nodulocystic acne, which is generally rare in black people, has been shown to be responsive to isotretinoin.[11]

Some authors have suggested that tretinoin may, in fact, be a primary treatment for postinflammatory hyperpigmentation. Data from a 40-week, double-blind, vehicle-controlled study of 54 black patients randomized to either tretinoin 0.1% cream or vehicle, showed that 92% of those treated with the active compound showed lightening of the facial hyperpigmented lesions, compared with only 57% of the control patients. Post-treatment colourimetry showed a 40% lightening of tretinoin-treated lesions vs. only 18% lightening in vehicle-treated lesions. Histological analysis showed epidermal melanin content from these lesions decreased by 23% following tretinoin therapy, but only 3% in response to the vehicle.[14]

Given the important role of tyrosinase in the development of postinflammatory hyperpigmentation, one might conclude that the observed effect of tretinoin on hyperpigmentation reflects some effect on this enzyme. However, a study of topical tretinoin 0.1% under occlusion for 4 days showed that while low tyrosinase activity in white skin was inducible by tretinoin, high tyrosinase activity in black skin could not be down-regulated by the topical retinoid.[15] Bulengo-Ransby *et al.* propose that the mechanism behind the effect observed in their study was inhibition of melanogenesis and redistribution or dispersion of epidermal melanin.[14]

Regardless of mechanism, tretinoin appears to have limited efficacy in reducing hyperpigmented macules. But this agent is itself an irritant and it is capable of inducing significant inflammation. In the study of tretinoin 0.1% cream for treatment of hyperpigmentation, 50% of those on active therapy had moderate to severe skin reactions, including erythema and desquamation. Although none of these patients experienced residual hyperpigmentation secondary to these reactions, this is a possibility one must keep in mind when treating acne in black patients.[1] Treatment-induced inflammation is a problem for all patients, but in black patients, there is the added risk of hyperpigmentation.

Adapalene in the treatment of acne among black South Africans

Adapalene has been shown to be equivalent in therapeutic efficacy with topical retinoids, but tends to be less irritating. Prior research has shown that this agent can address the hidden inflammatory component of acne in black patients.[10]

Materials and methods

The efficacy of adapalene 0.1% gel was assessed in 65 dark-skinned African patients, aged 12–30, in an open, non-comparative 12-week trial. The patients all had mild to moderate facial acne grades 1–5, as defined by the Leeds scoring system.[17] They were instructed to apply the medication once daily. Non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodules, cysts) lesions found on the forehead, both cheeks and chin were counted at the baseline visit and later at 4, 8, and 12 weeks, and global acne scores were made (on a scale of 1–10 where 0 = no acne). Safety evaluation, performed on each visit, was based on assessments of erythema, dryness, scaling, burning sensation, pruritus and oiliness. All of these parameters were ranked on a scale ranging from 0 to 3, where 0, 1, 2, 3 corresponded to none, mild, moderate, and severe, respectively.

Results

A total of 44 subjects completed the trial and all three follow-up visits. Adapalene 0.1% showed clear efficacy against both inflammatory and non-inflammatory lesions. The mean total facial lesion count decreased from 120 at baseline, to 80 by week 4, 60 at week 8, and 40 by completion of the study. Non-inflammatory lesions decreased from a mean of 75 at baseline to 30 by week 12; inflammatory lesion counts declined from a mean of 40 at the outset of treatment to 10 by week 12 (fig. 1). The decline in mean number of lesions from visit to visit ranged from 46 to 72%, and in most cases, there was clear improvement in cosmesis (fig. 2).

Effects on hyperpigmentation

As would be expected in an African population, many of our patients had some degree of acne-associated hyperpigmentation at baseline. We attempted to assess the effect of adapalene 0.1% on postinflammatory hyperpigmentation by selecting five hyperpigmented lesions on each patient and following the colour changes over the course of the 12 weeks.

None of the patients completing the treatment course had increases in hyperpigmentation. At baseline, 20% of the lesions we identified were characterized as highly pigmented. In two-thirds of these cases, patients experienced reductions in both number of hyperpigmented macules and density of the hyperpigmentation to a degree that is comparable to what has been observed for topical tretinoin (figs 3, 4).

Safety and tolerability

Unlike tretinoin, however, adapalene was far less likely to produce irritation, inflammation, or skin dryness. In our satisfaction survey of patients completing the treatment course, 80% of patients agreed or strongly agreed with the statement, 'product did not irritate the skin'. Only 5% of patients strongly

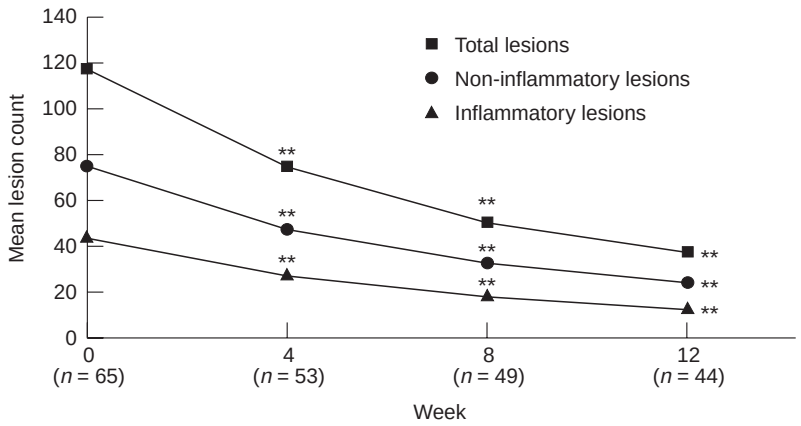

fig. 1 Decline in inflammatory lesion counts. $^{**}P < 0.01$ vs. baseline.

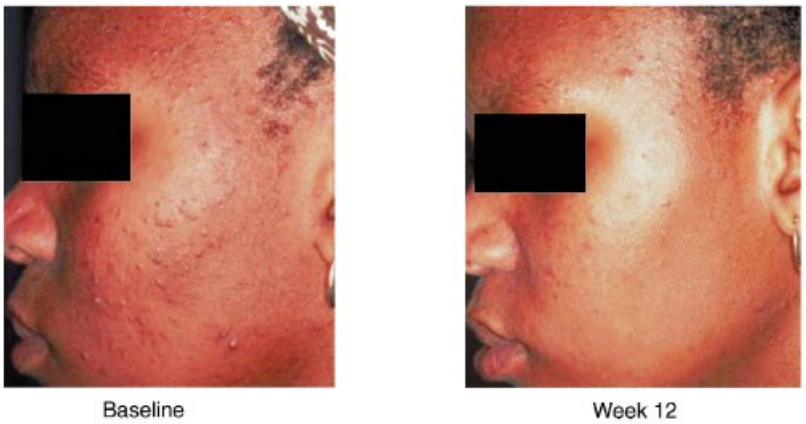

fig. 2 Visual improvement.

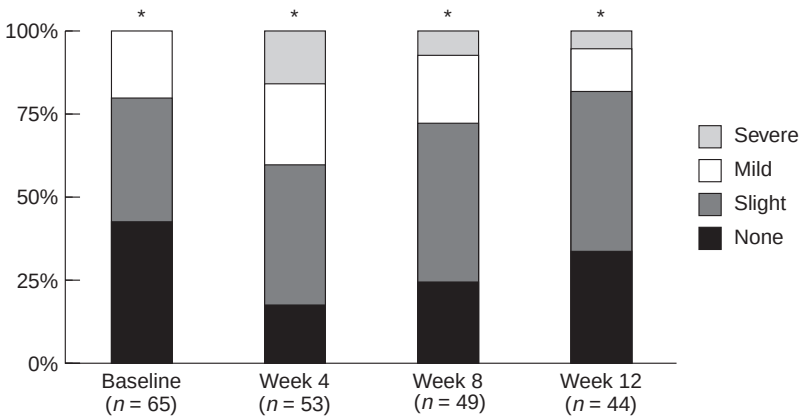

fig. 3 Change in hyperpigmentation severity. *$P < 0.01$ vs. baseline.

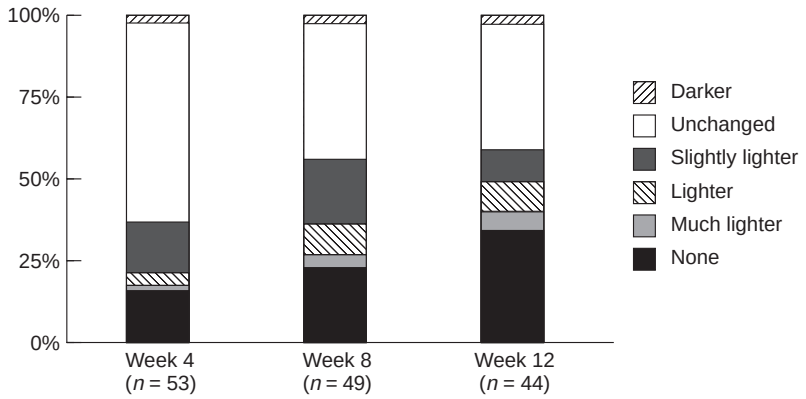

fig. 4 Change in hyperpigmentation: colouration.

disagreed with this statement. There were no systemic side effects observed in these patients during or after treatment with adapalene.

Discussion

Acne vulgaris, though as common among black people as among white people worldwide, can manifest somewhat differently among black individuals and other people of colour. Though the primary lesions may not appear to be as severe, this can mask considerable inflammation. Black skin is particularly prone to postinflammatory hyperpigmentation, and this is often more cosmetically problematic for patients than the primary acne lesions themselves.

The ideal acne therapy is one that can limit the inflammatory component of the disease, thus preventing the hyperpigmentation, as well as resolving existing hyperpigmented macules. While this optimal agent has yet to be developed, there is evidence that retinoids can be of some benefit. Tretinoin, though capable of reducing hyperpigmentation in some cases, can also

be highly irritating, and this in itself can induce post-treatment hyperpigmentation.

Our study of adapalene 0.1% gel in a sample of black South Africans with mild to moderate acne vulgaris, showed that this topical agent is effective in reducing both inflammatory and non-inflammatory acne lesions. It was safe, well tolerated, and highly acceptable to patients. Effective control of formation of new inflammatory acne lesions can prevent acne-associated hyperpigmentation. Our data suggest that adapalene can both prevent and reduce acne-associated hyperpigmentation.

There is a paucity of data on the prevalence and specific manifestations of acne vulgaris among black and other dark-skinned people. While it appears that the therapies proven effective and safe among white people will also be similarly effective in darker-skinned individuals, it is clear that the problem of hyperpigmentation specific to dark skin types warrants further research and increased attention on the part of the manufacturers of dermatological drugs.

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